IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Lehman *et al.*

Serial No.: 09/821,139

Filed: March 29, 2001

For: NASAL ADMINISTRATION OF AGENTS FOR THE TREATMENT OF GASTROPARESIS

Confirmation No.: 5628

Group Art Unit: 1616

Examiner: Haghighatian, M.

Attorney Docket No.: 7960-131

DECLARATION UNDER 37 C.F.R. § 1.132 OF ANASTASSIOS D. RETZIOS

Commissioner for Patents
PO Box 1450
Alexandria, Virginia 22313-1450

Sir:

I, Anastassios D. Retzios, declare that:

1. I am a co-inventor of the invention claimed in the above-identified U.S. patent application.

2. I earned a Bachelors of Science (B.S.) degree from the Aristotelian University of Thessaloniki, Thessaloniki, Greece in 1976. I attended the University of Edinburgh in Edinburgh, Scotland from 1977 to 1982 where I earned a Doctor of Philosophy (Ph.D.). My curriculum vitae is attached hereto at **Exhibit A**.

3. In my professional capacity I have been responsible for clinical project management for pharmaceutical products from program development to implementation, including FDA submission and approval in the United States. In addition, I have been responsible for management of various clinical research teams in Europe. I am familiar with the technical field of the invention claimed in the above-identified patent application.

4. I have authored and co-authored 29 scientific papers that have been published in journals such as, *Blood*, *Thrombosis Research*, *Circulation*, *Journal of Biological Chemistry* and the *Journal of Laboratory and Clinical Medicine*, among others.

5. Questcor Pharmaceuticals, Inc. ("Questcor") is the assignee of the above-identified application. Questcor is a corporate entity formed by the merger of RiboGene, Inc. ("RiboGene") and Cypros Pharmaceutical Corp., in November 1999. It is my understanding that Shire U.S., Inc., and GloboMax LLC have recently assigned their respective rights in the above-identified application to Questcor.

6. From March 1999 until November 1999, I was Director of Clinical Operations at RiboGene, where my duties included the organization of a clinical and regulatory department and development of departmental Standard Operating procedures.

7. From November 1999 to June 2001, I was Senior Director of Clinical Research and Development at Questcor. In my professional capacity at Questcor, my main area of responsibility was the clinical development of therapeutic agents in the areas of gastroenterology, chemotherapy and neurology.

8. From June 2001 to the present, I have been a consultant to Questcor.

9. I have reviewed the specification of the above-identified patent application, as well as the claims currently pending in the Application. I have also reviewed the final office action, mailed November 5, 2002 (hereinafter, the "final office action") in connection with the above-identified patent application, and the following references cited therein:

    a. U.S. Patent No. 4,624,965, to Wenig;

    b. Physician's Desk Reference entry for Reglan®;

    c. Packing inserts for Pramidin®; and

    d. Marketing Authorization for Pramidin®, published in the official gazette of the Italian government.

10. In summary, the document "Pramidin Marketing Authorization", presented as IDS Reference AD in the file history of the above-identified patent application, contains no dosage information, no information regarding duration of treatment, and no suggestion of how one would utilize intranasally administered metoclopramide for treating symptoms of gastroparesis. Additionally, I believe that it would have been surprising to one familiar with the field that intranasally administered metoclopramide was able to treat gastroparesis at least as effectively as orally-administered metoclopramide. Finally, it would also have been surprising to one familiar with the field that intranasally administered metoclopramide did not result in adverse

nasopharyngeal events in a significant portion of the patient pool, when applied in the dosages, and over the durations, claimed in the above-identified patent application.

11. I have reviewed the document referred to as "Pramidin Marketing Authorization", which was published in the Official Gazette of the Italian Government ("Gazzetta Ufficiale Della Repubblica Italiana") in December 1997. The document does not contain any description of dosages, or duration of treatment. Accordingly, one familiar with the field would not have been able to deduce an effective method of treating gastroparesis through intranasal administration of metoclopramide from what is disclosed in Pramidin Marketing Authorization.

12. I have also reviewed the excerpt from the Physician's Desk Reference that describes the product Reglan®, referred to herein as Robins, which is cited in the final office action. One familiar with the field, at the time the application was first filed, would have understood generally that the efficacy of an oral protocol relative to an intranasal protocol is drug-specific, and therefore would not have predicted that the same protocol would be effective for both an oral and an intranasal administration. Accordingly, one familiar with the field would not have assumed that dosages and durations of treatment disclosed by Robins for an intranasally administered application of metoclopramide for treating gastroparesis would have been equally effective with an intranasal version. This is because, typically, oral and intranasal routes of administration have different properties from one another.

13. Furthermore, at the time that the above-identified patent application was filed, the pharmacokinetics of intranasally administered metoclopramide over the timescale of several weeks were not known to one familiar with the field.

14. Additionally, based on my understanding of the known toxicity of metoclopramide when administered in doses of 10 mg q.i.d., (see, for example, the teaching of adverse central nervous system effects at page 9 of the entry for Reglan® from the Physicians' Desk Reference), it would have been reasonably expected that metoclopramide administered intranasally in doses of 10 mg and 20 mg q.i.d., (*i.e.*, in doses of 40–80 mg per day) for periods up to 8 weeks, would give rise to adverse CNS effects in a significant proportion of a patient pool.

15. Thus, based on the teachings of Pramidin Marketing Authorization, either alone, or in combination with Robins, one familiar with the field could not have predicted that intranasally administered metoclopramide would be successful for treating

gastroparesis. In particular, it was not known whether a dosage regime of 10 mg q.i.d. intranasally would be effective in treating gastroparesis, and it was not known whether a dosage regime of 20 mg q.i.d. intranasally would be too toxic to be tolerated.

16. One familiar with the field would not have predicted the efficacy of intranasally administered metoclopramide for treating gastroparesis, as revealed by the results of a clinical trial presented herein. At the time of carrying out the clinical trial, one familiar with the field would also not have predicted that intranasally administered metoclopramide would be tolerated by the patient pool. In particular, one familiar with the field would have predicted that the intranasal administration of metoclopramide would result in adverse nasopharyngeal events in a significant portion of the patient pool, when applied in the dosages, and over the duration explored in a clinical trial described hereinbelow.

17. During the course of my employment at Questcor, I was involved in supervising a clinical trial that compared the pharmacokinetics and safety of 10 mg and 20 mg doses of metoclopramide nasal spray with orally administered 10 mg metoclopramide tablets in patients with diabetic gastroparesis, in single and multiple doses (four times daily, before meals and at bedtime). Some aspects of this clinical trial are described in the above-identified patent application, at pages 12–22 of the specification as filed. Other aspects of the clinical trial are presented in **Exhibit B**, attached hereto.

18. The data from the clinical trial was evaluated using both an "intent to treat," and a "per protocol" analysis. After protocol violators had been excluded, similar results were observed in the per protocol analysis to those that had been obtained in the intent to treat analysis. *See* Table 2 at page 16 of the specification as filed of the above-identified patent application.

19. In the per protocol analysis, a significant difference was observed in the Total Symptom Score between baseline and week six for both the nasal 10 mg ($p = 0.026$) and nasal 20 mg ($p = 0.008$) cohorts compared to the oral 10 mg group.

20. In the intent to treat analysis, there was a statistically significant difference in the change from baseline in the Total Symptom Score between the nasal 20 mg and oral 10 mg cohorts at week six ($p = 0.026$). *See* Table 1 at page 15 of the specification as filed of the above-identified patent application. In addition, both the nasal 10 mg and nasal 20 mg groups had better mean total symptom scores than those in the oral 10 mg

group. Specifically, compared to the oral 10 mg group, the score was 2.5 and 3.8 points better for nasal 10 mg and nasal 20 mg, respectively.

21. The summary of mean change in Total Symptom Score from baseline to week six using an intent to treat analysis is provided in Table 3 at page 17 of the specification as filed of the above-identified patent application. For all three groups, the mean Total Symptom Score decreased by more than 15 points from baseline. The nasal 10 mg and nasal 20 mg cohorts showed greater improvement in Total Symptom Score than the oral 10 mg group.

22. The adjusted mean change from baseline to week six for each of the six symptoms using an intent to treat analysis is provided in Table 4 at page 18 of the specification as filed of the above-identified patent application. There was a statistically significant difference for three symptoms in the change in score from baseline to week six between the nasal 20 mg and oral 10 mg groups. These three symptoms were: loss of appetite ($p = 0.109$), feeling full after eating a small amount of food ($p = 0.010$), and persistent fullness after eating ($p = 0.003$). There was also a statistically significant difference between the nasal 10 mg and oral 10 mg groups for one symptom: feeling full after eating a small amount of food ($p = 0.021$). Accordingly, and surprisingly, nasally administered metoclopramide was found to be superior to orally administered metoclopramide in at least one patient symptom.

23. The results of this study indicate that metoclopramide nasal spray 10 mg and 20 mg have superior efficacy over the oral 10 mg tablets for treating gastroparesis as measured by at least one symptom. This was unexpected because, at the time that the study was carried out, the behavior of metoclopramide administered intranasally for durations studied in the trial was not known.

24. One familiar with the field would have expected adverse nasopharyngeal events that would precipitate withdrawal from treatment in a significant fraction of the patient population. However, as detailed hereinbelow, this was not the case.

25. Overall, approximately 63% of patients (56 out of 89) reported at least one adverse event. There was no statistically significant difference among treatment groups in terms of the number of patients experiencing an adverse event. *See* **Exhibit D**, attached hereto. There were no deaths reported in the study.

26. The number of drug related adverse events was higher in the 10 mg and 20 mg nasal metoclopramide groups (33 and 38, respectively) than in the oral 10 mg group (13 such events), see **Exhibit E**, attached hereto.

27. Three patients discontinued the trial due to an adverse event. Of these, two patients received nasal 20 mg metoclopramide, and one patient received oral 10 mg metoclopramide. One patient each in the nasal 20 mg and oral 10 mg cohorts discontinued due to severe restlessness, drowsiness and mild headache. The patient receiving oral 10 mg metoclopramide developed symptoms on Day 3 and discontinued study on Day 6. The patient receiving nasal 20 mg metoclopramide developed symptoms on Day 2 and the study drug was discontinued on Day 5. The third patient received nasal 20 mg metoclopramide and discontinued it on Day 33 after developing a rash on his hands, chest, and arms on Day 22 as well as experiencing nasopharyngeal symptoms. The rash was categorized as moderate while the nasopharyngeal symptoms were considered mild. Thus, none of the patients who discontinued the study due to an adverse event did so because they had experienced an adverse nasopharyngeal reaction.

28. The severity of adverse events was categorized as mild, moderate, or severe, and defined as:

Mild adverse events were transient, required no special treatment, and did not interfere with the patient's daily activities.

Moderate adverse events introduced a low level of inconvenience or concern to the patient and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.

Severe adverse events interrupted a patient's usual daily activities and typically require systemic drug therapy or other treatment.

29. A summary of results for patients reporting treatment-emergent adverse events, by severity and by body system, is presented in **Exhibit F**, attached hereto.

30. A summary of results for patients reporting treatment-emergent drug-related adverse events, by body system, is presented in **Exhibit G**, attached hereto.

31. A breakdown of the reported adverse events by body system for adverse events that occurred in at least two patients is presented at **Exhibit H**, attached hereto.

32. A summary of the number of drug related adverse events categorized by severity for each treatment group is summarized in **Exhibit I**, attached hereto. When the intensity of the adverse event changed over time, the maximum intensity was recorded. The

higher number of total adverse events in the nasal metoclopramide cohorts compared to the oral metoclopramide cohort is due to the higher number of nasopharyngeal adverse events and the higher proportion of patients enrolled into the nasal cohorts. A greater proportion of patients treated with oral 10 mg metoclopramide graded their adverse event as moderate while the majority of adverse events reported by patients treated with either dose of nasal metoclopramide was categorized as mild. Thus, nasally administered metoclopramide seems to be generally better tolerated by patients than orally administered metoclopramide.

33. The severe adverse events reported in each of the three treatment groups for different bodily symptoms is summarized in **Exhibit J**, attached hereto. One report each of severe neurological events of drowsiness and restlessness occurred in both the oral 10 mg and nasal 20 mg cohorts. The only severe event related to the nasal passages (rhinorrhea) occurred in the nasal 10 mg cohort. Thus, there was no significant nasopharyngeal reaction in the intranasal cohorts.

34. The major difference between the nasal and oral routes of administration of metoclopramide was the occurrence of a significant number of adverse events related to the nasopharynx. However, none of these adverse events was severe, and none directly resulted in patient withdrawal from the study.

35. At study visits and by telephone contact, patients were asked to complete a questionnaire regarding five complaints specific to the nasopharynx, listed in **Exhibit K**. The questionnaire did not specify rhinorrhea which occurred in 2 patients treated with nasal 10 mg metoclopramide; one of these events was considered severe while the other was categorized as mild. Sixteen of the 35 patients (45.7 %) treated with nasal 10 mg metoclopramide, and 15 out of 36 patients (41.7 %) treated with nasal 20 mg metoclopramide experienced an adverse event in the nasopharynx compared to 1 out of 18 patients (5.6 %) treated with oral 10 mg metoclopramide. These differences between the nasal 10 mg and nasal 20 mg and oral 10 mg metoclopramide cohorts were statistically significant ($p = 0.004$ and 0.010, respectively). There appeared to be no statistically significant difference, however, between the proportion of patients with nasopharyngeal events treated with nasal 10 mg and 20 mg metoclopramide. All but two of the nasopharyngeal events were categorized as mild; one event each of nasal irritation and epitaxis in the nasal 20 mg cohort was categorized as moderate. No adverse event addressed in the nasopharynx questionnaire was considered severe. Of the five types of adverse events relating to

the nasopharynx, a significantly higher proportion of patients in the nasal 10 mg and nasal 20 mg than the oral 10 mg reported nasal irritation as an adverse event (p=0.010 for both comparisons). All adverse events recorded as nasal irritation were categorized as mild except one (nasal 20 mg group, categorized as moderate), see "respiratory system" on **Exhibit F** attached hereto. All of these events of nasal irritation except two (one in each nasal dose group) were considered as possibly or probably drug related by the Investigators, see **Exhibit I** attached hereto. The other two were considered unrelated. The differences between the nasal and oral cohorts for the other adverse events related to the nasopharynx were not statistically significant.

36. In summary, the 10 mg nasal and 20 mg nasal cohorts were expected to experience a greater number of nasopharyngeal related adverse events than the 10 mg oral patients, because of the duration of exposure and the concentration of metoclopramide in the nasal preparation. In particular, the dosages employed in the 10 mg nasal and 20 mg nasal groups were high enough that adverse nasopharyngeal effects would have been expected in a significant proportion of the patient pool. Additionally, the intra-nasal administration of metoclopramide for prolonged periods – up to 6 weeks – would have been expected by one familiar with the field to produce substantial adverse nasopharyngeal effects. Surprisingly, to the extent that these adverse events occurred, they did not necessitate withdrawal from the study. It was thus unexpected that only a small number of patients receiving nasal metoclopramide would withdraw from the study due to intolerable nasopharyngeal related adverse events.

37. A summary of mean pharmacokinetic parameters following a single dose at Day 1 is provided at **Exhibit L**, attached hereto.

38. A summary of mean pharmacokinetic parameters following multiple doses, at Day 42, is provided at **Exhibit M**, attached hereto.

39. On Days 1 and 42, there were no statistically significant differences between the pharmacokinetic parameters of the 20 mg nasal spray and 10 mg oral treatments. In terms of maximum observed concentration of metoclopramide, C_{max}, statistically significant differences between the 10 mg nasal spray and 10 mg oral treatment groups were observed on Days 1 and 42, respectively.

40. In terms of accumulation, the ratios of the areas under the plasma concentration-time curve over the dosing interval, τ, on Days 1 and 42, for the 10 mg oral, 10 mg nasal

and 20 mg nasal groups were approximately 2, for all treatments. This indicates that at steady-state, the average plasma concentration of metoclopramide after multiple doses was approximately twice that following a single dose administration.

41. In keeping with our secondary objective, there was no statistically significant pharmacokinetic/pharmacodynamic relationship between the change in the Total Symptom Score from baseline to end of study, and the area under the plasma concentration time curve up to the last quantifiable concentration, $AUC_{0\text{-last}}$, or C_{max} following multiple doses.

42. In summary, metoclopramide treatment was found to be generally safe and well tolerated under the protocols used in the study. There were no clinically meaningful changes in hematology, chemistry, urinalysis, or vital signs during the study. The safety profile between the metoclopramide nasal spray and oral tablets was found to be comparable.

43. In conclusion, it is my belief that it one familiar with the field would not have predicted that metoclopramide could provide effective relief from gastroparesis when administered intranasally in doses of 10 mg and 20 mg q.i.d. for durations of several weeks, because there was a lack of knowledge of the behavior of metoclopramide at the doses and durations recited in the claims of the instant invention, and because one familiar with the field would have expected a substantial proportion of the patient pool to have experienced adverse nasopharyngeal effects sufficient to deter continued use of the medication, and/or because a substantial proportion of the patient pool would have exhibited adverse CNS effects.

44. I, a co-inventor of the invention described and claimed in the above-identified patent application further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the above-identified patent application or any patent issuing thereon.

Date: 8-17-03

Respectfully submitted,

Anastassios D. Retzios, Ph.D.

EXHIBIT A

Curriculum Vitae of Dr. Anastassios D. Retzios

Anastassios D. R tzi s, Ph.D.
2417 Canyon Lakes Drive, San Ramon, CA 94583
Tel: (818) 507-5541[Work]; (925) 735-7474 [Home]
E-mail address (personal): adretzios@home.com

Extensive experience in clinical project management from program development to implementation, submission and approval. Experience in overall project management and familiarity with most areas of drug or biologics development. Excellent administrative, management and communication skills; capable of organizing committed project teams and streamlining departmental organization and administration.

POSITIONS HELD

Jun 2001 - Present	Baxter BioScience, Glendale, California

Director, Clinical Development-Global

Duties include:

- Development of clinical strategy, master clinical plans for all products in development in
- Compilation of project timelines and budgets in association with Clinical Operations, Biostatistics and Data Management
- Development of clinical protocols in association with Clinical Project Managers and Medical Directors
- Supervision of authoring of Clinical Study Reports and Expert Reports in association with Clinical Project Managers and Medical Writing
- Assembly of Clinical Advisory Boards and Data Monitoring and Safety Boards in concert with Medical Directors
- Participation in Project Management Teams and Portfolio Assessment
- Participation in due diligence for potential inlicensing candidates
- Management of European Operations and European Clinical Research Team based in Vienna, Austria and Munich, Germany

Mar 1999 – Jun 2001 Questcor Pharmaceuticals, Inc. Hayward, California

Senior Director, Clinical Research and Development (Questcor Pharmaceuticals, Inc: Nov 1999 – Present)

Director of Clinical Operations (RiboGene, Inc. – Mar 1999 – Nov 1999)

Questcor Pharmaceuticals, Inc resulted from the merger of RiboGene, Inc (Hayward, CA) and Cypros Pharmaceutical Corporation (Carlsbad, CA)

- Main area of responsibility is the clinical development of in-licensed, acquired or in-house developed therapeutic agents in the areas of gastroenterology, chemotherapy and neurology.

- Accomplishments/responsibilities included:
  - Organization of clinical and regulatory department at RiboGene, Inc.
  - Development of departmental SOPs for both Ribogene, Inc. and Questcor Pharmaceuticals
  - Maintenance of continuous contact and collaboration with corporate partners both in the US, Europe and Asia (Korea) regarding ongoing or planned clinical development projects that led to submissions in various countries
  - Development of clinical protocols in various indications (delayed onset emesis in chemotherapy, migraine treatment)
  - Supervision of contract research organizations (CROs) that resulted in on-time and on-budget implementation of the development of Emitasol (intranasal metoclopramide)
  - Authoring of clinical development plans for various compounds considered for inlicensing
  - Compilation of annual and long-range departmental budgets
  - Supervision of clinical research personnel
  - Maintenance, prosecution and filing of all patents for the discovery and development program for Questcor Pharmaceuticals
  - Led several business development projects leading to stable and profitable alliances between Questcor and other pharmaceutical companies (Ahn-Gook, Seoul, Korea – Faber.Kramer, Houston, TX, US)
  - Completed detailed due diligence (both for manufacturing and clinical research) and participated in the reorganization efforts preceding and following the merger of Cypros and RiboGene

Oct 1991- Mar 1999 Alpha Therapeutic Corporation, Los Angeles, California

Associate Director, Clinical Research (Aug 1998 – Mar 1999)
Clinical Project Manager I – III (Oct 1991 – Jul 1998)

- Responsible for clinical development of coagulation/anticoagulation and anti-inflammation products.
- During a period of progressive increase in project and departmental responsibilities:
  - Directed multiple clinical research projects at any given time
  - Authored clinical development plans, clinical protocols, investigator brochures and analysis plans
  - Authored appropriate sections of IND and PLA/BLA submissions to the FDA
  - Compiled project and department budgets
  - Supervising clinical project managers, research associates and other project administrative personnel
- Submitted clinical reports that led to marketing approvals in the US and/or EU of:

- AlphaNine® SD in Hemophilia B; Profilnine® in Hemophilia B; Alphanate® in Hemophilia A
- Directed clinical studies in:
  - Hemophilia A and B, von Willebrand's disease, renal failure and hereditary angioedema
- Developed the continuing education program of the clinical research department
- Involved in feasibility assessment and clinical program development of products in sickle cell disease, anticoagulation, deep venous thrombosis, pulmonary hypertension, inflammation and others
- Involved in Project Management
  - Project Team Leader, overseeing all areas of development including research, manufacturing, QA/QC, clinical development and marketing
- Trained extensively in GCP, GMP, Personnel Management and Interpersonal Communications

Aug 1990- Sep 1991 **School of Pharmacy and Comprehensive Cancer Center, University of Southern California, Los Angeles, California.**

Senior Research Associate

Responsibilities included pharmacokinetic and pharmacodynamic determinations for various chemotherapeutic compounds, development of new analytical and methods and teaching: During this period:

- Determined pharmacokinetics and pharmacodynamics of locoregional application of several chemotherapeutic agents in Phase I and II clinical studies.
- Developed testing methodology, which allowed detection of infused compounds and their metabolites.
- Determined pharmacokinetics and pharmacodynamics of novel cancer chemotherapeutic agents in animal models.
- Supervised three graduate students.
- Taught courses on high- performance and conventional chromatographic techniques as well as computer-assisted experimental data analysis to graduate students

Feb 1987- Jul 1990 **Department of Biochemistry, School of Medicine, University of Southern California, Los Angeles, California.**

Research Associate

Duties included:

- The pharmaceutical development of naturally occurring thrombolytic and anticoagulant peptides and enzymes.
- Responsibilities included:
  - Purification and sequencing of fibrin-degrading enzymes of various venoms
  - Determination of their thrombolytic and hemostatic potential

- Structure/function characterization
- Effects on the human coagulation and fibrinolysis systems
- Estimation of kinetic constants with a number of natural and synthetic substrates
- Development of mid-to-large scale purification process in order to provide enough material for animal pharmacology/toxicology work

- Biochemical characterization of:
  - Extracellular matrix-dissolving enzymes
  - Platelet aggregation inhibitors.
- Other responsibilities included:
  - Monthly progress reports to funding company (Marion Laboratories).
  - Presentations to members of the Marion Laboratories Project Team
  - Training and supervision of a number of research technicians, graduate and work-study students.
- Obtained patent on the use of certain venom-derived thrombolytic enzymes (US Patent 5,260,060 -Nov. 9, 1993).

May 1983 - Jan 1987 **Department of Medicine, Division of Hematology, School of Medicine, University of Southern California, Los Angeles, California**

Postdoctoral fellow

The main emphasis of postdoctoral work was on the detailed characterization of proteins involved in the early stages of blood clot formation. In the process of the study:

- Determined the structural/functional relationships of the light chain of human high molecular weight kininogen, and its mechanism of interaction with other components of the extrinsic pathway of blood coagulation.
- Determined the kinetics of activated factors XI, XII, kallikrein for several artificial chromogenic substrates
- Developed a two-substrate assay for quick and accurate estimation of these factors in plasma.

Also worked on pituitary hormone involvement in obesity, in collaboration with the Endocrinology Division. Developed HPLC methods for the analysis of pituitary extracts and identification of selected hormones.

EDUCATION

1977-1982 **Department of Molecular Biology, University of Edinburgh Edinburgh, Scotland, United Kingdom**

Degree obtained: **Ph.D.**

Thesis centered on the effects of natural selection on molecular evolution.

1969-1976 **School of Sciences and Mathematics, Aristotelian University of Thessaloniki, Thessaloniki, Greece.**

Degree obtained: **B.S.**
Major: Natural Sciences

SOCIAL

1973-1975	Served in the Greek Army, Engineers' Corps
1978-1979	Secretary of the Hellenic Society of Edinburgh and Heriot-Watt Universities
1979-1980	Secretary of the Post-Graduate Students' Union (PGSU) of Edinburgh University.
1980-1981	President of the Post-Graduate Students' Union of Edinburgh University. Member of the Edinburgh University's Student Affair committee and Union Funds Allocation Committee.
1984-1985	Technical Correspondent and Newsletter Editor of the Sanyo Computer Users Group of Los Angeles (SUGLA).
1985-1987	President of the MS-DOS/Sanyo Users Group of Los Angeles
1989-1991	Editor and correspondent in the University of Southern California microcomputer publication "Random Access"

LIST OF PUBLICATIONS

1. Retzios, A. D. and Thatcher, D. R. (1979): Chemical basis of the electrophoretic variation observed at alcohol dehydrogenase locus of *Drosophila melanogaster*. ***Biochimie***, 61, 701-704.

2. Thatcher, D. R. and Retzios, A. D. (1980): Mutations affecting the structure of *Drosophila* Alcohol Dehydrogenase. ***Protides Biol. Fluids. Proc. Colloq.*** 28, 157-160.

3. Retzios, A. D. and Thatcher, D. R. (1981): Characterization of the Adh^{f} and Adh^{us} alleloenzymes of *Drosophila melanogaster* (fruitfly) alcohol dehydrogenase. ***Biochem. Soc. Trans.*** 9, 298-299.

4. Retzios, A. D., Rosenfeld, R. and Schiffman, S. (1984): Determination of the functional groups in human HMWK. ***Circulation*** 70, II-352 -abstract.

5. Retzios, A. D., Rosenfeld, R. and Schiffman, S. (1985): Different binding sites for prekallikrein and factor XI in the light chain of human high molecular weight kininogen. ***Blood***, 66, 342a -abstract.

6. Schiffman, A. D., Rosenfeld, R. and Retzios, A. D. (1986): Interaction of factor XI and sulfatide. ***Thromb. Res.*** 41, 575-580.

7. Retzios, A. D., Rosenfeld, R. and Schiffman, S. (1987): Effects of chemical modification on the surface- and protein-binding properties of the light chain of human high molecular weight kininogen. ***J. Biol. Chem.*** 262, 3074-3081.

8. Retzios, A. D., Rosenfeld, R. and Schiffman, S. (1988): Enzymes of the contact phase of blood coagulation: Kinetics with various chromogenic substrates and a two substrate assay for the joint estimation of plasma prekallikrein and factor XI. ***J. Lab. Clin. Med.*** 112, 560-566.

9. Bray, G. A., Shimizu, H., Retzios, A. D. and York, D. A. (1988): Studies on the metabolic basis for obesity: Sympathetic activity, adrenalectomy and reduced acetylation of MSH. In ***Hormones, Thermogenesis and Obesity***, Ed., H. Lardy, F. Stratman, Elsevier Science Publishing Co., New York, pp 245-256.

10. Retzios, A. D. and Markland, F. S. (1988): A direct-acting fibrinolytic enzyme from the venom of *Agkistrodon contortrix contortrix*: Interactions with various components of the human blood and fibrinolysis systems. ***Thromb. Res.*** 52, 541-552.

11. Markland, F. S., Guan, A. and Retzios, A. D. (1988): A direct-acting fibrinolytic enzyme from southern copperhead venom. ***Fibrinolysis*** 2, Suppl. 1, 67 -abstract.

12. Retzios, A. D. and Markland, F. S. (1988): Two-step HPLC purification of a fibrinolytic enzyme from Florida cottonmouth venom. Protein Society, 2nd Symposium, San Diego, U.S.A., p77 -abstract.

13. Bray, G. A., Shimizu, H., Retzios, A. D., Shargill, N. J. and York, D. A. (1989): Reduced acetylation of melanocyte stimulatory hormone (MSH): a biomedical explanation for the yellow obese mouse. In ***Obesity in Europe***, Ed., P. Bjoutorp, S. Rossner, John Libbey and Co., London, pp. 230-241.

14. Retzios, A. D, and Markland, F. S. (1989): Fibrinolytic enzyme from the venom of *Agkistrodon piscivorus conanti* (Florida cottonmouth). Protein Society, 3rd Symposium, Seattle, U.S.A., M99 -abstract.

15. Guan, A. L., Retzios, A. D. and Markland, F.S. (1989): A hemorrhagic (basement membrane degrading) zinc metalloproteinase from southern copperhead venom. Matrix Metalloproteinase Conference, Destin, Florida, U.S.A -abstract.

16. Retzios, A. D. and Markland, F. S. (1990): HPLC-based two-step purification method of fibrinolytic enzymes from the venom of *Agkistrodon*

contortrix contortrix and *Agkistrodon piscivorus conanti*. ***Protein Expression and Purification*** 1, 33-39.

17. Trikha, M., Retzios, A. D. and Markland, F. S. (1990): A novel platelet aggregation inhibitor from southern copperhead venom. 11th International Congress on Thrombosis -abstract.

18. Retzios, A. D. and Markland F. S. (1990): Three distinct fibrinolytic enzymes from the venom of *Crotalus basiliscus basiliscus*. Fourth Symposium of the Protein Society, San Diego, California -abstract.

19. Retzios, A. D. and Markland F. S. (1990): Chemical modification studies of Accfib, a fibrinolytic enzyme from the venom of *Agkistrodon contortrix contortrix*. Fourth Symposium of the Protein Society, San Diego, California -abstract.

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EXHIBIT B

Details Of Clinical Trial Of Metoclopramide Nasal Spray For Treating Gastroparesis

1. The clinical trial was a multi-center, controlled, randomized, open-label, parallel design study in patients with diabetic gastroparesis.

2. The primary objective of the clinical trial was to characterize the pharmacokinetics of 10 mg and 20 mg metoclopramide nasal spray, (registered under the trade name Emitasol®), and 10 mg oral metoclopramide tablets (marketed under the trade name Reglan®), when administered to patients with diabetic gastroparesis, in single doses, and multiple doses q.i.d. (four times daily, before meals and at bedtime).

3. The secondary objectives of the clinical trial were:
   i) to compare the safety of the 10 mg and 20 mg doses of metoclopramide nasal spray to 10 mg metoclopramide tablets administered orally; and
   ii) to assess the pharmacokinetic/pharmacodynamic relationships of the 10 mg and 20 mg doses of metoclopramide nasal sprays, and the 10 mg metoclopramide tablet taken orally.

4. Patients were selected for study according to the following inclusion criteria.
   Patients were:

   a. Males, and non-pregnant, non-lactating females;

   b. Eighteen years of age or older;

   c. Able to give informed consent;

   d. Able to understand the instructions and administer the nasal spray; and

   e. Willing to discontinue current treatment for diabetic gastroparesis (if any) from the start of the seven day washout, *i.e.*, a period of abstention from a potentially interacting medication, prior to the initial symptom assessment through the end of the six week treatment period;

   Additionally,

   f. Non-sterile females were required to use adequate birth control during the course of the study;

   g. Patients had received a prior diagnosis of Type I or Type II diabetes;

h. Patients were required to display stable treatment for fourteen days prior to starting the study medication, for all medical treatments for other concurrent conditions;

i. The Investigator had ruled out other causes of gastric stasis; symptoms, including, for example, mechanical obstruction;

During the study, patients were selected according to the following considerations:

j. Patients must have had a total symptom score of between 8 and 20 on each of the assessment scales (SAQ or Symptom Assessment Questionnaire, and IAQ or Investigator's Assessment Questionnaire);

k. A minimum of two out of the six symptoms must have been rated moderate (2) or higher on each of the SAQ or IAQ scales;

l. No clinically significant chemistry or hematology parameters (with the exception of plasma glucose) were determined by the Investigator; and

m. Estimated creatinine clearance was greater than 40 mL/min.

5. Patients were selected for study according to the following exclusion criteria.

Patients were disqualified if they had:

a. Any physical or psychological condition that the Investigator believed would interfere with the patient's ability to participate in the clinical study;

b. Used tricyclic antidepressants, meperidine or methadone within the past 30 days, and during the study;

c. Other disorders that can cause abnormal gastrointestinal motility such as amyloidosis, neuromuscular diseases, collagen vascular diseases, alcoholism, uremia, malnutrition, untreated hypothyroidism or uncontrolled and frequent migraine headaches;

e. History of chronic pancreatitis, gross malabsorptive syndromes, inflammatory bowel disease, acquired immunodeficiency syndrome, severe cardiac or hepatic disease or severe pulmonary diseases;

f. Parkinson's disease;

g. History of any esophageal or gastric surgery;

h. Presence of mechanical gastrointestinal obstruction, hemorrhage and/or perforation;

i. Pheochromocytoma;

j. History of hypersensitivity or toxicity with metoclopramide use including but not limited to, acute dystonic reactions and tardive dyskinesia;

k. Other investigational agents such as study drugs within 30 days of enrollment in the instant study; and

l. Known history of illicit drug use within the past year.

Additionally,

m. Patients must have discontinued the use of the following agents seven days prior to the initial symptom assessment, and refrain from their use for the entire six week study treatment period:

i. Prokinetic agents, *e.g.*, misoprostil, cisapride, domperidone, or erythromycin;

ii. Cholinergic agents, *e.g.*, bethanechol, donepezil, pyridostigmine, tacrine;

iii. Agents with significant anticholinergic effects, *e.g.*, atropine;

iv. Chronic use of narcotic analgesics (greater than four doses per week for three weeks preceding the study);

v. Orally administered β-agonists (inhaled β-agonists were permitted);

vi. Spasmolytics, *e.g.*, oxybutynin and flavoxate;

vii. Ondansetron, granisetron and dolasetron;

viii. Dopamine agonists, *e.g.*, levodopa, pergolide, amantadine; and

ix. Monoamine oxidase inhibitors.

6. Written informed consent was obtained from each subject. The investigators obtained ethical review board approval for the protocol from Integ Review, 1825 Fortview Road, Suite 105, Austin, TX 78704.

7. There were 89 eligible patients who enrolled in the clinical study. The patients were randomized into three cohorts to receive, respectively, metoclopramide nasal spray 10 mg, metoclopramide nasal spray 20 mg, or oral metoclopramide 10 mg tablets. The numbers within each cohort are shown in **Exhibit C**, attached hereto. All treatments were to be taken four times daily before meals and at bedtime, for six weeks. There was a seven day washout from potentially interacting medication prior to randomization of the eligible patients to one of the three treatment groups.

8. Eighty-two (82) patients completed the study. Seven patients failed to complete the study. Of the 82 patients who completed the clinical study, 79 (96.3%) received all

doses of metoclopramide; the remaining three patients were non-compliant in some respect. The three cohorts were balanced in the number of patients who received study drug through different study timepoints. A summary of the extent of drug exposure on a biweekly basis for the three treatments is shown in **Exhibit C**, attached hereto.

9. The analysis of safety included all patients who were randomized and received at least one dose of study drug. The safety data were reviewed for all adverse events including those associated with early withdrawal. The adverse events were evaluated by treatment group and intensity (mild, moderate, or severe). Adverse events associated with nasal symptoms were evaluated in all patients.

10. Safety precautions included permitting patients to terminate the study early, taking measurements of adverse events, vital signs, conducting physical examinations, reviewing medical histories, and conducting clinical laboratory tests.

11. According to the protocol, patients were assessed at three study visits and by telephone in the intervals between the study visits. The planned study visits were: Days 1 and 2 (visit 1), Day 14 ± 3 (visit 2), and Day 42 and 43 ± 3 (visit 3). The schedule for telephone assessments were: Day 7 ± 1, Day 21 ± 1, Day 28 ± 1, and Day 35 ± 1. The safety assessments at both visits and via telephone included SAQs and targeted nasopharyngeal assessment questionnaires. The laboratory tests for chemistry, hematology and urinalysis were obtained only at the three study visits. On Day 1, blood samples were obtained prior to the first dose of metoclopramide, then at 0.5, 1, 1.5, 2, 3, 4, 8, 10, 12, 14 and 24 hours post dose for the determination of metoclopramide plasma concentrations. Following the 24 hour blood sample, patients received the second dose of their assigned study medication and were discharged with instructions to use the medication four times daily before meals and at bedtime. Safety and symptom assessments were completed on Days 7, 14, 21, 28, 35 and 42. In addition, on Days 14 and 42, patients returned for a single blood sample for determination of metoclopramide concentrations.

12. Plasma samples were stored at –20 °C until analysis. Analysis included the extraction of metoclopramide and an internal standard (procainamide) from human plasma. Samples were analyzed by HPLC with fluorescence detection. Pharmacokinetic parameters were calculated by non-compartmental analysis of the plasma concentration-time data at Day 1 and Day 42 using standard software program

(WinNonlin). The analysis was conducted using actual times for determination of all pharmacokinetic parameters.

13. A Symptom Assessment Questionnaire (SAQ) was used to assess symptom frequency and therapeutic efficacy before, during, and at the conclusion of treatment. Patients were asked to rate the frequency of each of six target symptoms. The six target symptoms were: i) nausea; ii) vomiting; iii) loss of appetite; iv) feeling bloated; v) feeling full after eating a small amount (early satiety); and vi) persistent fullness. Patients assigned each symptom an ordinal frequency score of zero to four.

14. An Investigator's Assessment Questionnaire (IAQ) was used to assess symptom severity and therapeutic efficacy before, during, and at the conclusion of treatment. The six target symptoms were: i) nausea; ii) vomiting; iii) loss of appetite; iv) feeling bloated; v) feeling full after eating a small amount (early satiety); and vi) persistent fullness. The Investigator assigned each symptom an ordinal frequency score of zero to four.

15. Symptom Assessment Questionnaires and Investigator's Assessment Questionnaires were completed at baseline and once per week during the six week treatment period: Days 7, 14, 21, 28, 35 and 42, respectively.

16. The primary efficacy endpoint was the change from baseline to the end of the study in the Total Symptom Score (TSS). The total symptom score was the sum of the Symptom Assessment Questionnaire (SAQ) and the Investigator's Assessment Questionnaire (IAQ). If a patient terminated prematurely from the study, the last available TSS was used.

17. Secondary efficacy endpoints involved the following:

    a. Changes from baseline in the weekly total symptom score;

    b. For each individual symptom, combined severity and frequency score;

    c. Percentage of responders;

    d. Summary of the glycemic control markers, fructosamine and HbA-1c, in the form of descriptive statistics on the change from baseline.

18. The data was evaluated using both an "intent to treat" and a "per protocol" analysis. The intent to treat analysis used a population comprising all patients who received at

least one dose of trial drug. The per protocol analysis used a population that included patients who did not significantly violate, or significantly deviate from the protocol.

19. Eleven patients were excluded from the per protocol analysis: two patients did not save a SAQ and IAQ at week 6; three patients failed to record their time of administration according to study protocol; and six patients took prohibited medication.

EXHIBIT C

Number Of Patients Who Received Study Through Different Timepoints

	Oral -10 mg	Nasal - 10 mg	Nasal - 20 mg
Enrolled	18	35	36
Duration of treatment At least 1 day	18 (100%)	35 (100%)	36 (100%)
At least 14 days	17 (94.4%)	33 (94.3%)	34 (94.%)
At least 28 days	17 (94.4%)	33 (94.3%)	34 (94.4%)
At least 42 days	16 (88.9%)	31 (88.6%)	32 (88.9%)

EXHIBIT D

Patients Who Experienced At Least One Adverse Event

	Oral - 10 mg	Nasal - 10 mg	Nasal - 20 mg	Total
Number enrolled	18	35	36	**89**
Patients with at least one adverse event	11 (61.1%)	22 (62.9%)	23 (63.9%)	**56** (62.9%)

EXHIBIT E
Drug Related Adverse Events

	Oral - 10 mg	**Nasal - 10 mg**	**Nasal - 20 mg**
Patients Enrolled	18	35	36
Patients with at least 1 drug related adverse event	7 (38.9%)	18 (51.4%)	17 (47.2%)
Number of drug related adverse events	13	33	38
Number of drug related adverse events related to nasopharynx	0	22	21
Number of drug related adverse events other than nasopharynx	13	11	17

Exhibit F

Summary of Patients Reporting Treatment Emergent Adverse Events* By Severity

	Oral 10 mg. (N = 18)						Nasal 10 mg. (N = 35)						Nasal 20 mg. (N = 36)					
	Mild		Moderate		Severe		Mild		Moderate		Severe		Mild		Moderate		Severe	
Body System/Adverse Event	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Body as a Whole																		
ACCIDENTAL INJURY	0	0.0	0	0.0	0	0.0	1	2.9	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
ALLERGY SYMPTOMS	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.8	0	0.0
ASTHENIA	0	0.0	1	5.6	0	0.0	1	2.9	0	0.0	0	0.0	1	2.8	0	0.0	0	0.0
CHEST PAIN	0	0.0	0	0.0	0	0.0	1	2.9	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
CHILLS	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.8	0	0.0
FEVER	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.8	0	0.0
FLU SYNDROME	0	0.0	1	5.6	0	0.0	0	0.0	0	0.0	0	0.0	1	2.8	2	5.6	0	0.0
GENERALIZED EDEMA	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.8	0	0.0	0	0.0
HEADACHE	2	11.1	1	5.6	0	0.0	2	5.7	0	0.0	0	0.0	4	11.1	0	0.0	1	2.8
INFECTION	0	0.0	1	5.6	0	0.0	3	8.6	1	2.9	0	0.0	1	2.8	1	2.8	0	0.0
PAIN	1	5.6	1	5.6	0	0.0	0	0.0	0	0.0	0	0.0	1	2.8	2	5.6	0	0.0
Cardiovascular System																		
HYPERTENSION	0	0.0	1	5.6	0	0.0	0	0.0	0	0.0	0	0.0	1	2.8	0	0.0	0	0.0
PALPITATION	0	0.0	0	0.0	0	0.0	1	2.9	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
VASOVAGAL REACTION	0	0.0	0	0.0	0	0.0	1	2.9	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Digestive System																		
ANOREXIA	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.8
BLOATING	1	5.6	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.8	1	2.8
CONSTIPATION	0	0.0	1	5.6	0	0.0	1	2.9	0	0.0	0	0.0	0	0.0	1	2.8	0	0.0
DIARRHEA	0	0.0	0	0.0	0	0.0	2	5.7	0	0.0	1	2.9	1	2.8	0	0.0	0	0.0
DYSPEPSIA	0	0.0	1	5.6	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
EARLY SATIETY	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.8	0	0.0

*If a patient reported an adverse event more than once only the most severe occurrence is reported

Body System/Adverse Event	Oral 10 mg. (N = 18)						Nasal 10 mg. (N = 35)						Nasal 20 mg. (N = 36)					
	Mild		Moderate		Severe		Mild		Moderate		Severe		Mild		Moderate		Severe	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
FLATULENCE	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.8	0	0.0	0	0.0
GINGIVITIS	0	0.0	1	5.6	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.8	0	0.0
INCREASED APPETITE	0	0.0	0	0.0	0	0.0	0	0.0	1	2.9	0	0.0	0	0.0	0	0.0	0	0.0
LIVER FUNCTION TESTS ABNORMAL	0	0.0	0	0.0	0	0.0	1	2.9	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
NAUSEA	0	0.0	1	5.6	2	11.1	0	0.0	0	0.0	0	0.0	0	0.0	2	5.6	0	0.0
TOOTH DISORDER	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.8	0	0.0	0	0.0
VOMITING	1	5.6	0	0.0	1	5.6	1	2.9	0	0.0	0	0.0	0	0.0	1	2.8	0	0.0
Hemic and Lymphatic System																		
LEUKOPENIA	0	0.0	0	0.0	0	0.0	1	2.9	1	2.9	0	0.0	0	0.0	0	0.0	0	0.0
LYMPHOCYTOSIS	0	0.0	0	0.0	0	0.0	1	2.9	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Metabolic and Nutritional Disorders																		
HYPERGLYCEMIA	0	0.0	0	0.0	0	0.0	0	0.0	1	2.9	0	0.0	0	0.0	0	0.0	0	0.0
HYPOGLYCEMIA	0	0.0	1	5.6	0	0.0	1	2.9	0	0.0	0	0.0	0	0.0	0	0.0	1	2.8
WEIGHT GAIN	1	5.6	0	0.0	0	0.0	0	0.0	1	2.9	0	0.0	0	0.0	0	0.0	0	0.0
Musculoskeletal System																		
SPRAIN	0	0.0	1	5.6	0	0.0	0	0.0	1	2.9	0	0.0	0	0.0	0	0.0	0	0.0
Nervous System																		
DIZZINESS	2	11.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.8	0	0.0	0	0.0
HYPERKINESIA	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.8	0	0.0	0	0.0
IRRITABLE	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.8	0	0.0
NERVOUSNESS	0	0.0	0	0.0	1	5.6	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.8
SOMNOLENCE	0	0.0	0	0.0	1	5.6	0	0.0	0	0.0	0	0.0	2	5.6	2	5.6	1	2.8

*If a patient reported an adverse event more than once only the most severe occurrence is reported

Body System/Adverse Event	Oral 10 mg. (N = 18)						Nasal 10 mg. (N = 35)						Nasal 20 mg. (N = 36)					
	Mild		Moderate		Severe		Mild		Moderate		Severe		Mild		Moderate		Severe	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Respiratory System																		
BRONCHITIS	0	0.0	0	0.0	0	0.0	0	0.0	1	2.9	0	0.0	0	0.0	1	2.8	0	0.0
EPISTAXIS	0	0.0	0	0.0	0	0.0	6	17.1	0	0.0	0	0.0	1	2.8	1	2.8	0	0.0
NASAL IRRITATION	0	0.0	0	0.0	0	0.0	11	31.4	0	0.0	0	0.0	10	27.8	1	2.8	0	0.0
NASAL SORES	0	0.0	0	0.0	0	0.0	2	5.7	0	0.0	0	0.0	1	2.8	0	0.0	0	0.0
NASAL TENDERNESS	0	0.0	0	0.0	0	0.0	3	8.6	0	0.0	0	0.0	6	16.7	0	0.0	0	0.0
PHARYNGITIS	0	0.0	0	0.0	0	0.0	0	0.0	1	2.9	0	0.0	0	0.0	0	0.0	0	0.0
PNEUMONIA	0	0.0	0	0.0	0	0.0	0	0.0	1	2.9	0	0.0	0	0.0	0	0.0	0	0.0
RHINORRHEA	0	0.0	0	0.0	0	0.0	1	2.9	0	0.0	1	2.9	2	5.6	0	0.0	0	0.0
SINUS IRRITATION	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.8	0	0.0
SINUS PAIN	1	5.6	0	0.0	0	0.0	3	8.6	0	0.0	0	0.0	1	2.8	0	0.0	0	0.0
Skin and Appendages																		
RASH	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.8	0	0.0
Special Senses																		
TASTE PERVERSION	1	5.6	0	0.0	0	0.0	0	0.0	1	2.9	0	0.0	0	0.0	1	2.8	0	0.0
Urogenital System																		
CYSTITIS	0	0.0	1	5.6	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
HEMATURIA	1	5.6	0	0.0	0	0.0	1	2.9	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

*If a patient reported an adverse event more than once only the most severe occurrence is reported

Exhibit G

Summary of Patients Reporting Treatment Emergent Drug Related Adverse Events* Sorted By Body System

Body System/Adverse Event	Oral 10 mg (N = 18) N	(%)	Nasal 10 mg (N = 35) N	(%)	Nasal 10 mg (N = 36) N	(%)
Number of Patients With At Lease One Drug Related AE	7	38.9	18	51.4	17	47.2
Number of Patients With No Drug Related AE	11	61.1	17	48.6	19	52.8
Body as a Whole						
ASTHENIA	1	5.6	1	2.9	0	0.0
CHEST PAIN	0	0.0	1	2.9	0	0.0
HEADACHE	2	11.1	2	5.7	3	8.3
Cardiovascular System						
PALPITATION	0	0.0	1	2.9	0	0.0
Digestive System						
CONSTIPATION	1	5.6	0	0.0	1	2.8
DIARRHEA	0	0.0	1	2.9	1	2.8
FLATULENCE	0	0.0	0	0.0	1	2.8
INCREASED APPETITE	0	0.0	1	2.9	0	0.0
NAUSEA	2	11.1	0	0.0	0	0.0
VOMITING	1	5.6	0	0.0	0	0.0
Hemic and Lymphatic System						
LEUKOPENIA	0	0.0	1	2.9	0	0.0
LYMPHOCYTOSIS	0	0.0	1	2.9	0	0.0

*Only the first occurrence of each adverse event is reported for each patient

Body System/Adverse Event	Oral 10 mg (N = 18) N	(%)	Nasal 10 mg (N = 35) N	(%)	Nasal 10 mg (N = 36) N	(%)
Metabolic and Nutritional Disorders						
WEIGHT GAIN	1	5.6	1	2.9	0	0.0
Nervous System						
DIZZINESS	2	11.1	0	0.0	1	2.8
HYPERKINESIA	0	0.0	0	0.0	1	2.8
IRRITABLE	0	0.0	0	0.0	1	2.8
NERVOUSNESS	1	5.6	0	0.0	1	2.8
SOMNOLENCE	1	5.6	0	0.0	5	13.9
Respiratory System						
EPISTAXIS	0	0.0	4	11.4	2	5.6
NASAL IRRITATION	0	0.0	10	28.6	10	27.8
NASAL. SORES	0	0.0	1	2.9	1	2.8
NASAL TENDERNESS	0	0.0	3	8.6	6	16.7
RHINORRHEA	0	0.0	1	2.9	1	2.8
SINUS PAIN	0	0.0	3	8.6	1	2.8
Skin and Appendages						
RASH	0	0.0	0	0.0	1	2.8
Special Senses						
TASTE PERVERSION	1	5.6	1	2.9	1	2.8

*Only the first occurrence of each adverse event is reported for each patient

EXHIBIT H

Adverse Events That Occurred In Two Or More Patients

	Oral - 10 mg	Nasal - 10 mg	Nasal - 20 mg
Enrolled	18	35	36
Body			
Asthenia	1 (5.6%)	1 (2.9%)	1 (2.8%)
Flu Syndrome	1 (5.6%)	0	3 (8.3%)
Headache	3 (16.7%)	2 (5.7%)	5 (13.9%)
Infection	1 (5.6%)	4 (11.4%)	2 (5.6%)
Pain	2 (11.1%)	0	3 (8.3%)
Digestive			
Bloating	1 (5.6%)	0	2 (5.6%)
Constipation	1 (5.6)	1 (2.9%)	1 (2.8%)
Diarrhea	0	3 (8.6%)	1 (2.8%)
Nausea	3 (16.7%)	0	2 (5.6%)
Vomiting	2 (11.1%)	1 (2.9%)	1 (2.8%)
Hemic & Lymphatic			
Leukopenia	0	2 (5.7%)	0
Metabolic & Nutritional			
Hypoglycemia	1 (5.6%)	1 (2.9%)	1 (2.8%)
Neurologic			
Dizziness	2 (11.1%)	0	1 (2.8%)
Somnolence	1 (5.6%)	0	5 (13.9%)
Respiratory			
Bronchitis	0	1 (2.9%)	1 (2.9%)
Epistaxis	0	6 (17.1%)	2 (5.6%)
Nasal irritation	0	11 (31.4%)	11 (30.6%)
Nasal sores	0	2 (5.7%)	1 (2.8%)
Nasal tenderness	0	3 (8.6%)	6 (16.7%)
Rhinorrhea	0	2 (5.7%)	2 (5.6%)
Sinus pain	1 (5.6%)	3 (8.6%)	1 (2.8%)
Special Senses			
Taste perversion	1 (5.6%)	1 (2.9%)	1 (2.8%)

EXHIBIT I
Adverse Events Categorized By Severity

	Oral - 10 mg	Nasal - 10 mg	Nasal - 20 mg
Patients Enrolled	18	35	36
Total Adverse events	29	57	63
Mild*	11 (37.9%)	45 (78.9%)	38 (60.3%)
Moderate*	13 (44.8%)	10 (17.5%)	24 (38.1%)
Severe*	5 (17.2%)	2 (4.4%)	6 (9.5%)

* The denominator for the percentage of adverse events by intensity is the total number of adverse events for that treatment group.

EXHIBIT J
Severe Adverse Events Categorized by Body System

	Oral – 10 mg	**Nasal – 10 mg**	**Nasal – 20 mg**
Patients Enrolled	18	35	36
Total Adverse Events	29	57	63
Severe Adverse Events			
Headache	0	0	1
Anorexia	0	0	1
Bloating	0	0	1
Diarrhea	0	1	0
Nausea	2	0	0
Vomiting	1	0	0
Hypoglycemia	0	0	1
Nervousness	1	0	1
Somnolence	1	0	1
Rhinorrhea	0	1	0
(Total Severe)	**5**	**2**	**6**

EXHIBIT K

Reported Adverse Events Of The Nasopharynx

	Oral - 10 mg	Nasal - 10 mg	Nasal - 20 mg
Patients Enrolled	18	35	36
Patients with ≥ 1 nasopharynx adverse event	1 (5.6%)	16 (45.7%)	15 (41.7%)
Type of nasopharynx adverse event			
Nasal irritation	0	12 (34.3%)	13(36.1%)
Nasal tenderness	0	3 (8.6%)	6(16.7%)
Bloody nose	0	5 (14.3%)	2(5.6%)
Sinus pain	1 (5.6%)	3 (8.6%)	1(2.8%)
Sores in or on nose	0	2 (5.7%)	1(2.8%)

EXHIBIT L

Mean Pharmacokinetic Parameters of Metoclopramide on Study Day 1 following a Single Dose

Treatment	N	C_{max} (ng/mL)	T_{max} (h)	AUC_{1-4} (ng h/mL)	AUC_{1-inf} (ngh/mL)	$t_{1/2}$ (h)
10mg Oral Tablet	18	36.41	1.72	265.52	304.09	6.89
10mg Nasal Spray	34	29.13	1.76	221.44	268.97	6.90
20mg Nasal Spray	35	48.78	1.81	359.10	412.12	7.63

EXHIBIT M

Summary of Mean Pharmacokinetic Parameters of Metoclopramide on Study Day 42 following Multiple Doses

Treatment	N	C_{max} (ng/mL)	T_{max} (h)	AUC_{1-4} (ng h/mL)	AUC_{1-inf} (ng h/mL)	$t_{1/2}$ (h)
10 mg Oral Tablet	17	61.21	1.19	481.11	564.44	8.44
10 mg Nasal Spray	31	41.11	1.48	411.05	515.79	8.86*
20 mg Nasal Spray	33	67.23	1.18	483.44	573.16	8.03**

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